Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis

Dewy van Hoogmoed¹,², Jaap Fransen², Gijs Bleijenberg¹ and Piet van Riel²

Abstract

Objectives. Fatigue is a frequently experienced and patient-relevant complaint in RA. Disease activity, anaemia and pain are regarded as disease-related factors that may lead to fatigue in RA. However, psychosocial factors may also play a role in maintaining severe fatigue. The objectives of this study were to determine the prevalence of severe fatigue in RA patients, to study patient perceptions of fatigue and to determine which disease-related factors and psychosocial factors are independently associated with fatigue severity.

Methods. For this study consecutive RA outpatients were enrolled (n = 228). The patients filled out questionnaires regarding fatigue using the Checklist Individual Strength (CIS), including psychosocial factors, pain and disability. The clinical data that were collected included ESR, CRP, haemoglobin level and 28-joint disease activity score (DAS-28). Chunk-wise backward linear regression was used for analysis.

Results. Severe fatigue (CIS ≥ 35) was experienced by 42% of the RA patients, and they perceived their fatigue as frustrating or exhausting. The severely fatigued RA patients scored worse on all measured psychosocial items, compared with patients without severe fatigue. Pain severity, role functioning, depressive mood, self-efficacy on fatigue, worrying, helplessness and non-restorative sleep were the factors most strongly associated with fatigue level.

Conclusions. A considerable proportion of RA patients had severe fatigue, with fatigue levels similar to chronic fatigue syndrome. Fatigue in RA was related to pain and functioning, not inflammation, as disease-related factors and to several psychosocial factors including coping and cognitions concerning fatigue.

Key words: Fatigue, Rheumatoid arthritis, Psychosocial factors, Inflammation, Physical disability.

Introduction

RA is an auto-immune disease that causes inflammation and damage of the synovial joints. Major patient complaints are pain, disability and fatigue. Serious fatigue is experienced by many patients with RA [1–3]. In as much as 40% of the patients, this fatigue is found to be persistent over 1 year, and in severity the fatigue is similar to the chronic fatigue syndrome [3].

In RA, fatigue generally is subscribed to disease-related factors, especially inflammation, anaemia and pain. However, it appears to be pain, rather than inflammation (acute-phase response, swollen joint count) that is related to fatigue [2, 3]. It also seems likely in RA that, like in other conditions such as disease-free breast cancer or FM, psychosocial factors play a role in explaining fatigue severity [4, 5]. Several quantitative studies found that, in addition to pain and disease activity, psychosocial factors were associated with fatigue level in RA patients [2, 6–10]. Some qualitative studies suggested that RA fatigue may incorporate cognitive and emotional elements [11, 12].

To get more insight into factors that are independently associated with fatigue in RA, multivariate analyses are needed, including multiple psychosocial factors in addition to disease activity measures and inflammation markers [7, 9, 10]. Although in two cross-sectional studies
pain is found to be strongly associated with fatigue [7, 9], these studies also report several different findings. Huys\textit{er et al.} [7] found that besides pain, gender and depressive symptoms are the best predictors of RA fatigue, whereas Riemsma \textit{et al.} [9] found that, complementary to pain, self-efficacy concerning RA symptoms and towards the ability to mobilize help as well as a problematic social support are the strongest predictors of RA fatigue. In contrast, Treharne \textit{et al.} [10] found that RA fatigue is best predicted by lower ESR level at baseline, perceptions of consequences of RA and self-efficacy over fatigue/mood 1 year earlier. Two of the studies used a visual analogue scale (VAS) for measuring fatigue severity [7, 10], one used a fatigue questionnaire but only included social support, self-efficacy and affective disorders as psychosocial factors [9].

Included in this study are both disease-specific measures and a comprehensive set of psychosocial correlates of fatigue that have been shown to be generally important in explaining fatigue in other chronic conditions [13, 14]. The possible determinants of RA fatigue were carefully selected based on determinants of fatigue in the chronic fatigue syndrome, disease-free breast cancer patients and patients with neuromuscular disorders as well as literature concerning RA fatigue [5, 14, 15]. Furthermore, a validated and reliable fatigue questionnaire [Checklist Individual Strength (CIS)] with an established cut-point for severe fatigue was used to measure fatigue severity [15].

The objectives of this study were to determine the prevalence of severe fatigue in RA patients, to assess patients’ perceptions about fatigue and to determine the independent association between fatigue severity and disease-related and psychosocial factors.

**Patients and methods**

**Recruitment procedure**

A total of 431 RA patients aged 18–75 years attending the outpatient rheumatology clinic of the Radboud University Nijmegen Medical Center were approached between June 2006 and October 2007 to participate in the current study. Two hundred and thirty (53%) patients were eligible and willing to participate. Two patients were excluded after the first measurement because of a sleep apnoea and a malignant lung tumour. All patients were diagnosed with RA by a rheumatologist according to the 1987 ACR classification criteria for RA. Allowed comorbidities were a secondary SS, regulated diabetes mellitus (normalized values of glucose and Hba1c), regulated thyroid disease (normalized values of free T4 and thyroid stimulating hormone), mild non-restrictive chronic pulmonary disease and a successfully treated not metastasized basal cell carcinoma or squamous cell carcinoma in the skin in the medical history. Patients with other rheumatic diseases (except for secondary SS), a history of malignancies or other comorbidities associated with chronic fatigue were excluded. The prevalence of clinical depression in the study population was 7%, which is in accordance with the prevalence in the general Dutch population (www.rivm.nl).

**Demographic and medical characteristics**

Demographic characteristics, disease characteristics and comorbidities were collected by research nurses using clinical research charts. Blood samples were taken to measure ESR, CRP and haemoglobin level. To determine the activity of RA, the 28-joint disease activity score (DAS-28) was scored by a rheumatologist or a specialized rheumatology nurse.

**Determinants of fatigue**

In this study, fatigue was the primary outcome measure. To identify determinants of fatigue, a multidimensional assessment method developed at the Expert Centre for Chronic Fatigue Nijmegen was used [15]. The multidimensional assessment method identifies dimensions relevant for fatigue. The dimensions that were originally found to be relevant for fatigue were psychological well-being, functional impairment, sleep disturbances, avoidance of physical activity, concentration, social functioning, self-efficacy and causal attributions [15]. Previously, this set of determinants has been slightly adapted to neuromuscular disorders and disease-free breast cancer patients [5, 14]. The determinants have been tested in chronic fatigue syndrome, neuromuscular diseases and post-cancer fatigue [5, 13, 14]. Treatment of fatigue based on these determinants has been found to be effective [16, 17]. Based on these determinants and the literature concerning factors related to RA fatigue, dimensions relevant for RA fatigue were added: age, gender and illness duration, RF, pain and disease activity, optimism and self-esteem (gathered under the determinant ‘behavioural factors’), coping with fatigue and catastrophizing were selected [2, 8, 10, 18, 19].

**Self-reported questionnaires**

**Fatigue.** Fatigue severity was measured using the fatigue severity subscale (CIS-fatigue) of the CIS (CIS20r) [15, 20]. Higher scores on the CIS-fatigue indicate a higher level of experienced fatigue. A score of >35 indicates severe fatigue, and is 2 s.d. above the mean score of healthy adults [21]. A score between 27 (mean score of healthy adults plus 1 s.d.) and 35 indicates a heightened level of fatigue [17]. The CIS-fatigue consists of eight items and all items are scored on a 7-point Likert scale. The CIS20r has proven to be a reliable and valid instrument in various conditions [5, 15, 20, 22, 23]. Previously, it was shown that the CIS20r is also reliable and valid in RA [24]. RA patients were divided into two groups, one with severe fatigue and one with heightened or normal fatigue, using the CIS-fatigue cut-point of >35. The Fatigue Quality List (FQL) was used to assess different perceptions of fatigue. It consists of 18 adjectives, and patients were instructed to mark which of the adjectives fit their experienced fatigue; multiple answers were possible [25]. The adjectives are subdivided into four categories: frustrating fatigue,
exhausting fatigue, frightening fatigue and pleasant fatigue.

Pain. Pain severity was measured with a Numerical Rating Scale (NRS) regarding pain in the current situation on a scale ranging from 0 (no pain) to 10 (violent pain), and using the bodily pain subscale of the Short-form Health Survey (SF-36).

Restrictions of daily functioning. Restrictions of daily functioning were determined using the HAQ Disability Index (HAQ-DI) and the subscales role functioning and physical functioning of the SF-36. The HAQ-DI, consisting of eight items, measures the influence that the disease has on daily life functioning [26]. The SF-36 was used to measure physical functioning ability and role functioning [27].

Psychological well-being and behavioural factors. Beck’s Depression Inventory for primary care (BDI-pc) was used to screen for clinical depression, and it consists of seven items [28]. A total score of ≥4 on the BDI-pc is suggestive of clinical depression. To measure psychological distress, the subscales anxiety, agoraphobia and depressive thoughts of the Symptom Check List 90 (SCL90) were used [29]. The mental health subscale of the SF-36 was also used. Self-esteem was measured with the Rosenberg Self-Esteem (RSE) scale consisting of 10 statements [30] and optimism was measured with the Life Orientation Test (LOT), consisting of 12 statements on a 5-point Likert scale [31].

Attributions and self-efficacy concerning fatigue. Beliefs regarding the somatic and non-somatic causes of fatigue were measured with a modified version of the Causal Attribution List (CAL) [32]. Based on a factor analysis performed in SPSS 16.0, the modified CAL-RA consisted of a somatic and a non-somatic factor, each containing three items. Cronbach’s-α of the somatic and the non-somatic factor was 0.71 and 0.74, respectively. Items were scored on a 4-point Likert scale. Self-efficacy concerning fatigue was measured with the Self-Efficacy Scale 28 (SES28), a 7-item questionnaire scored on a 4-point Likert scale [32].

Coping with fatigue. Coping strategies were determined with the Modified Pain Coping Inventory for Fatigue (MPCI-F). It is scored on a 4-point Likert scale and is based on the Pain Coping Inventory [33]. In the MPCI-F, ‘pain’ is replaced with ‘fatigue’. With this questionnaire the use of both passive and active coping strategies were measured [34].

Catastrophizing of fatigue. To determine catastrophizing (a negative orientation towards harmful stimuli), the Fatigue Catastrophizing Scale (FCS) was used. The FCS was derived from the Pain Catastrophizing Scale (PCS) [35], in which the word pain is replaced with ‘fatigue’.

Social support and functioning. Discrepancies between desired social support and actual support as well as negative social support were measured with the Social Support List Discrepancies (SSL-D) and the Social Support List Negative (SSL-N) [36]. The questionnaires consisted of 34 and 7 questions, respectively. Social functioning was measured with the equally named subscale of the SF-36.

Sleep. The subscale sleep disturbances of the SCL90 subscale was filled in by patients.

Self-reported physical activity. Patients were asked about their physical activity during the past week using the Questionnaire Physical Activity (QPA), in which patients reported the number of minutes they spend weekly on walking, cycling and on exercising.

Data analysis

Analyses were performed using Statistical Package for Social Sciences (SPSS) 16.0 for Windows. To replace missing values, single imputation was used on the condition of the data being missing at random. If only one or two observations of a variable were missing, values were imputed using group mean or median. To test univariately for differences between severely fatigued and not-severely fatigued RA patients, independent t-tests, Mann–Whitney U-tests and χ²-tests were performed as appropriate. Pearson or Spearman correlations were used to study correlations between fatigue severity as a continuous measure and disease-related and psychosocial factors.

Chunk-wise linear regression [37] was performed to reduce the number of variables to be considered and to achieve a parsimonious model. The dependent variable was fatigue severity according to the CIS-fatigue, the ‘chunks’ were sets of person-bound characteristics, disease-related variables, pain, restrictions in daily functioning, psychological well-being, behavioural factors, attributions and self-efficacy concerning fatigue, coping with fatigue, catastrophizing of fatigue, social support and functioning, sleep disturbances and self-reported physical activity. Multiple regressions with a backward selection procedure were performed to reduce the number of variables within each chunk. At last, to create the final model, a multiple regression with backward selection was performed on the remaining variables of the chunks.

Results

A total of 228 RA patients were included, and the patient characteristics are shown in Table 1.

Prevalence of severe fatigue

The mean CIS-fatigue severity score was 31.5 (s.d. 12.8). According to the CIS, most RA patients had a fatigue level that was higher than normal. As many as 96 RA patients (42%) met the cut-off point for severe fatigue (CIS-fatigue ≥ 35). Additionally, 46 patients (20%) experienced heightened fatigue levels (CIS-fatigue between 27 and 35). Since patients with a heightened fatigue level were assigned to the non-severely fatigued group for the
### Table 1: Comparisons between severely fatigued RA patients and not-severely fatigued RA patients and the association of fatigue with person-bound characteristics, medical/disease characteristics and psychosocial factors

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Variables (scale)</th>
<th>Total sample&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No fatigue&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Severe fatigue&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P</th>
<th>Correlation</th>
<th>CIS-fatigue P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-bound characteristics</td>
<td>Age</td>
<td>55.91 (10.78)</td>
<td>58.06 (9.96)</td>
<td>52.95 (11.21)</td>
<td>0.000</td>
<td>–0.25</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Female gender, n (%)</td>
<td>144 (63)</td>
<td>77 (58.33)</td>
<td>67 (69.79)</td>
<td>0.077</td>
<td>0.06</td>
<td>0.342</td>
</tr>
<tr>
<td>Medical variables</td>
<td>BMI</td>
<td>25.41 (23.21–27.77)</td>
<td>25.61 (23.06–27.57)</td>
<td>25.11 (23.30–27.97)</td>
<td>0.917</td>
<td>–0.007</td>
<td>0.913</td>
</tr>
<tr>
<td></td>
<td>Positive RF, n (%)</td>
<td>171 (75)</td>
<td>107 (81.10)</td>
<td>64 (66.70)</td>
<td>0.013</td>
<td>–0.25</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Illness duration, years</td>
<td>10 (6–17)</td>
<td>11 (7–17)</td>
<td>10 (5–17)</td>
<td>0.174</td>
<td>0.09</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>DAS-28 (0–10)</td>
<td>3.15 (1.22)</td>
<td>2.85 (1.09)</td>
<td>3.56 (1.28)</td>
<td>0.024</td>
<td>0.18</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>SF-36 bodily pain (0–100)</td>
<td>64.17 (19.84)</td>
<td>72.66 (16.90)</td>
<td>52.48 (17.57)</td>
<td>0.000</td>
<td>–0.57</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>SF-36 role functioning (0–100)</td>
<td>25.0 (0–100)</td>
<td>62.3 (25–100)</td>
<td>22.1 (0–25)</td>
<td>0.000</td>
<td>–0.56</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>SF-36 mental health (0–100)</td>
<td>76.23 (16.18)</td>
<td>80.64 (12.80)</td>
<td>70.17 (18.31)</td>
<td>0.000</td>
<td>–0.38</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin, mmol/l</td>
<td>8.20 (0.72)</td>
<td>8.20 (0.71)</td>
<td>8.20 (0.74)</td>
<td>0.975</td>
<td>0.02</td>
<td>0.729</td>
</tr>
<tr>
<td></td>
<td>Pain NRS pain severity (0–10)</td>
<td>4.30 (2.43)</td>
<td>3.24 (2.00)</td>
<td>5.76 (2.22)</td>
<td>0.000</td>
<td>–0.55</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>SF-36 social functioning (0–100)</td>
<td>39 (35–44)</td>
<td>38.5 (34–44)</td>
<td>39 (35–48)</td>
<td>0.470</td>
<td>0.08</td>
<td>0.219</td>
</tr>
</tbody>
</table>

<sup>a</sup>Numbers are mean (s.d.), median (P25–P75) or n (%) as denoted; <sup>b</sup>CRP levels of <5 are scored as 0; <sup>c</sup>scored on a reversed scale, a higher score means better functioning and less pain. TJC28: tender joint count of 28 joints.
Correlates of fatigue

**Univariate analyses.** Severely fatigued patients were on average younger, whereas there was no clear gender difference (Table 1). The proportion of patients negative for RF was larger in the severely fatigued group. The DAS-28, the number of tender joints, swollen joints and the general health rating were significantly worse in the severely fatigued RA patients. However, ESR, CRP and haemoglobin level did not differ between the two groups, nor did they correlate with fatigue severity. In contrast, severely fatigued RA patients had worse pain scores. Similar results were found for the three measures of functioning.

Regarding the psychosocial variables, results were consistent. Compared with non-severely fatigued patients, fatigued RA patients scored worse on all measured psychosocial items. For most variables, the difference between fatigued and non-severely fatigued RA patients was significant, and most variables correlated significantly with the CIS-fatigue score (Table 1). The highest univariate correlations were found with pain and disability, and with depressive thoughts, anxiety, mental health, worrying, helplessness, self-efficacy, sleep disturbances and social functioning. In contrast, distraction and social support discrepancy were not significantly correlated with fatigue severity.

**Multivariate analyses.** After performing backward regression on each chunk, the following variables remained: age, RF, TJC28, pain severity, bodily pain, physical functioning, role functioning, depressive mood, self-esteem, somatic attributions and self-efficacy on fatigue, coping strategies worrying and resting, helplessness and magnification of fatigue, social functioning, sleep disturbances and self-reported physical activity (Table 3).

With the final backward analysis, the chunks containing person-bound characteristics and behavioural factors became obvious from the model. The model following from this backward analysis contained age, RF, pain severity, bodily pain, physical and role functioning, depressive mood, self-efficacy on fatigue, the coping strategy of worrying, magnification of fatigue and sleep disturbances (Table 3).

**Discussion**

Our study shows that a large proportion of the RA patients (42%) experienced severe fatigue. While severely fatigued RA patients perceived their fatigue as frustrating or exhausting, non-severely fatigued RA patients generally experienced fatigue as a normal and pleasant phenomenon. In univariate analysis, fatigue severity was not associated with inflammation or anaemia, but was associated with pain severity functioning and with nearly all psychosocial factors. In multivariate analysis, fatigue severity was associated with age, RF, pain, daily functioning, depressive thoughts, self-efficacy concerning fatigue, worrying, magnification of fatigue and sleep disturbances. This multivariate analysis shows that fatigue in RA is not just related to physical factors or depression. Psychosocial factors rather than inflammation-related factors seem to play an important role in fatigue severity in RA.

The high prevalence of severe fatigue in this study confirms previous findings [3, 38, 39]. The advantage of our study is that, by use of a generic fatigue questionnaire, fatigue severity can be given a meaning by comparing with other conditions. A fatigue score of ≥35 indicates a fatigue level similar to that of chronic fatigue syndrome [21]. On average, RA patients have higher fatigue levels than healthy controls and cancer survivors, and lower levels of fatigue compared with patients with multiple sclerosis [5, 20].

In contrast, with non-severely fatigued RA patients, severely fatigued RA patients reported that the fatigue they experienced was a frustrating or exhausting one. The differences in fatigue experience indicate that the severe fatigue, as experienced by a substantial number of the RA patients, is indeed not comparable with the normal and pleasant fatigue experienced by healthy persons or RA patients with a non-severe fatigue.

The results from this study clearly show that psychosocial factors are also relevant to fatigue severity in RA. Especially depressive thoughts, self-efficacy concerning fatigue, coping with fatigue and catastrophizing of fatigue were important psychosocial factors. Only a small percentage of the RA patients in this study could be classified as having clinical depression. In literature it is found that fatigue in RA is related to several psychological factors besides pain, disease activity and depression [8, 10]. Our results support the idea that depression is not the only psychological factor that contributes to fatigue. Although in several studies 13–20% of the RA patients

<table>
<thead>
<tr>
<th>TABLE 2 Perceptions of fatigue in RA patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience of fatigue</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>FQL</td>
</tr>
<tr>
<td>Frustrating</td>
</tr>
<tr>
<td>Exhausting</td>
</tr>
<tr>
<td>Frightening</td>
</tr>
<tr>
<td>Pleasant</td>
</tr>
</tbody>
</table>

Numbers are median (P25–P75); ‘no severe’ fatigue was defined as a CIS < 35 and ‘severe’ fatigue was defined as a CIS ≥ 35.
<table>
<thead>
<tr>
<th>Dimensions, in chunks</th>
<th>Variables in chunk</th>
<th>Variables entered in final backward regression analysis$^{a}$</th>
<th>β</th>
<th>Variables in model$^{b}$</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-bound characteristics</td>
<td>Age</td>
<td>Age</td>
<td>−0.25***</td>
<td>Age</td>
<td>−0.12***</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>Sex</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical variables</td>
<td>RF</td>
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<td>−0.24***</td>
<td>RF</td>
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<td></td>
<td>SJC28</td>
<td>TJC28</td>
<td>0.29***</td>
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<td>Pain</td>
<td>NRS pain severity</td>
<td>NRS pain severity</td>
<td>0.30***</td>
<td>NRS pain severity</td>
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<td>SF-36 bodily pain</td>
<td>SF-36 bodily pain</td>
<td>−0.35***</td>
<td>SF-36 bodily pain</td>
<td>−0.17**</td>
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<td>Restrictions on daily functioning</td>
<td>HAQ-DI</td>
<td>SF-36 physical functioning</td>
<td>−0.25***</td>
<td>SF-36 physical functioning</td>
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<td>SF-36 role functioning</td>
<td>SF-36 role functioning</td>
<td>−0.41***</td>
<td>SF-36 role functioning</td>
<td>−0.13*</td>
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<td>Psychological well-being</td>
<td>BDI-pc</td>
<td>SCL90 depressive thoughts</td>
<td>0.35***</td>
<td>SCL90 depressive thoughts</td>
<td>0.15**</td>
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<td></td>
<td>SCL90 anxiety</td>
<td></td>
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<td></td>
<td>SCL90 agoraphobia</td>
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<td></td>
<td>SF-36 mental health</td>
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<tr>
<td>Behavioural factors</td>
<td>LOT (optimism)</td>
<td>RSE</td>
<td>−0.25***</td>
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<td></td>
<td>RSE (self-esteem)</td>
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<tr>
<td>Attributions and self-efficacy about fatigue</td>
<td>CAL somatic</td>
<td>CAL somatic</td>
<td>−0.22***</td>
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<td></td>
<td>CAL non-somatic</td>
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<tr>
<td></td>
<td>SES28</td>
<td>SES28</td>
<td>−0.43***</td>
<td>SES28</td>
<td>−0.20**</td>
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<td>Coping with fatigue</td>
<td>MPCI-F worrying</td>
<td>MPCI-worrying</td>
<td>0.38***</td>
<td>MPCI-worrying</td>
<td>0.21*</td>
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<td>MPCI-F retreating</td>
<td>MPCI-resting</td>
<td>0.12*</td>
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<td>MPCI-F fatigue transformation</td>
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<td>MPCI-F reducing demands</td>
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<tr>
<td>Catastrophizing of fatigue</td>
<td>FCS-ruminaton</td>
<td>FCS-helplessness</td>
<td>0.55***</td>
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<td></td>
<td>FCS-magnification</td>
<td>FCS-magnification</td>
<td>−0.23**</td>
<td>FCS-magnification</td>
<td>−0.11*</td>
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<td>Social support and functioning</td>
<td>SSL-N</td>
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<td></td>
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<tr>
<td></td>
<td>SF-36 social functioning</td>
<td>SF-36 social functioning</td>
<td>−0.50***</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sleep</td>
<td>SCL90 sleep disturbances</td>
<td>SCL90 sleep disturbances</td>
<td>0.40***</td>
<td>SCL90 sleep disturbances</td>
<td>0.14**</td>
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<td>Physical activity (self-reported)</td>
<td>QPA</td>
<td>QPA</td>
<td>−0.15*</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

$^{a}$These variables remained in the chunk after backward regression analysis was performed on that specific chunk; $^{b}$these variables remained in the model after the final backward regression analysis. *P < 0.05, **P < 0.01, ***P < 0.001, NS: not significant. x: the variable representing the chunk was entered in the final backward regression analysis but stepped out.
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are found to be depressed, in the sample of this study only 7% of the patients were found to be clinically depressed [40, 41]. The small number of depressed patients is less than that usually found in other studies, but this might be explained by the relatively healthy population in our study [40]. Disease activity and ESR were quite low as well as the functional impairments. Besides pain, these factors are found to be related to depression in patients with RA [42–44]. Nevertheless, although the prevalence of clinical depression was not heightened, many patients experienced depressive feelings, and in RA fatigue depressive thoughts (‘depressiveness’) do seem to play a role.

Restrictions in daily functioning are an important factor in fatigued patients. In our study, role functioning and physical functioning were more important than disability as measured with the HAQ-DI; however, these concepts are closely interconnected. The close correlation of the measures may have led to the result that only two of the measures ‘survived’ in the multivariate analysis, where in fact they are quite interchangeable. In previous studies, the association between function and fatigue in RA was also found [3, 38].

Also, in line with previous studies, indications were found that patients with severe fatigue have a lower self-efficacy, and thus thought themselves of being less able to influence their fatigue [7, 9]. Taking this into account, it seems logical that this group also shows more catastrophizing of their fatigue. They experience more feelings of helplessness concerning their fatigue, and show more rumination on fatigue and magnify their fatigue than the not-severely fatigued patients. Although our study results are cross-sectional, they are in line with the finding of Tack [11] in a qualitative study that one of the consequences of fatigue is an overwhelming sense of helplessness. Additionally, Covic et al. [45] found that in RA patients helplessness concerning pain significantly correlates with passive coping strategies, whereas passive coping with pain significantly relates to a higher pain level. The results of our study show a similar pattern for fatigue, as the passive coping strategy ‘worrying’ (about fatigue) is an important factor in relation to fatigue level.

Of the disease-related factors, pain was strongly associated with fatigue, and disease activity and tender joint count were moderately associated with fatigue, whereas inflammation markers, swollen joint count and anaemia were not. The association between the severity of pain experienced by RA patients and the fatigue these patients experience was one of the highest correlations found in this study. Fatigued RA patients experience significantly more pain statistically and clinically [46]. The relation between pain and fatigue is often found in other studies [2, 6–8, 38, 47] and was also found to be one of the best predictors of RA fatigue [38]. In one study, although pain was found to be univariately associated with fatigue severity, when a multiple linear regression analysis was performed pain was no longer a significant predictor of fatigue [10].

Swollen joint count, ESR, CRP and haemoglobin levels did not correlate well with fatigue severity and did not differ much between the fatigued RA patients and the not-severely fatigued RA patients. Although most patients identify disease activity as the primary cause of their fatigue [6], and a heightened CRP level is found to be linked to worse scores for energy and fatigue level in RA patients [47], our finding that disease activity does not play a prominent role in fatigue level has been found in previous studies [2, 3]. The relation between inflammation and fatigue is at least not as strong as is often assumed [7]. Disease activity is probably an eliciting factor of RA fatigue; however, as shown by the results of this study, psychosocial factors also play an important role. We suggest that psychosocial factors may be important in the perpetuation of fatigue and some of them may cause patients to be more susceptible to becoming fatigued, e.g. elicited by disease activity.

Causality cannot be determined due to the cross-sectional design of this study. Due to the descriptive nature of this study, a comprehensive set of variables was taken into account to analyse which factors possibly influence RA fatigue. Similar previous studies assessed different limited sets of psychosocial factors and used different fatigue measurement instruments, and therefore found different results [7, 9, 10]. The results of our study integrates those findings by using a comprehensive set of psychosocial factors and shows that several of the factors found by these different studies are independently correlated with fatigue severity in RA.

A limitation of this study was that the number of variables measured was high in relation to the number of participants. However, by performing chunk-wise regression this problem has been reduced. No indicators of collinearity were found, e.g. unexpectedly outlying regression coefficients during the analyses. An additional point of attention is possible multicollinearity between the predictors. Predictors within chunks do tend to correlate with each other and may in fact be exchangeable. The factors most strongly correlating with each other are the NRS pain severity measure and the Bodily pain scale of the SF-36 (<–0.71, P < 0.001). Nevertheless, both factors remain in the multiple regression analysis, each contributing a substantial part. Since bodily pain still contributed significantly to fatigue levels in RA independently of pain severity, this indicates that although factors might be related with each other, multicollinearity does not seem to be a problem here.

Psychosocial factors, pain and functioning, rather than inflammation-related factors, seem to play an important role in fatigue severity in RA. These factors might be the reason that fatigue is present, also in high levels, while disease activity is low. Due to this, cognitive behavioural therapy (CBT) might be an appropriate therapy to treat RA fatigue where usual care does not suffice. It is known from other chronic conditions that CBT, especially directed at reducing fatigue, is an appropriate treatment with good results [16, 17, 48]. Also in RA, results of CBT on fatigue are promising, although the effects in the two studies on CBT on RA fatigue were small [49, 50]. Longitudinal research is necessary to get further insight...
into the most important psychosocial factors influencing fatigue level as well as the course of fatigue over a longer period. The results found in this study confirm that a large number of RA patients suffer from a severe fatigue that is experienced as a serious problem. Fatigue in RA is primarily related to pain and functioning, not inflammation, and to several psychosocial factors including coping and cognitions concerning fatigue.

**Rheumatology key messages**
- A substantial number of RA patients experience a debilitating fatigue.
- Pain, functioning and psychosocial factors, including coping and cognitions, are more important in RA fatigue than inflammation.

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